

CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE  
TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

FOLPET

SB 950-044, Tolerance #00191

July 24, 1986

Revised May 4, 1987

Revised January 8, 1988

Revised December 1, 1988

I. DATA GAP STATUS

Combined rat:	No data gap, possible adverse effect
Chronic dog:	No data gap, no adverse effect
Onco mouse:	No data gap, possible adverse effect
Repro rat:	No data gap, no adverse effect
Terato rat:	No data gap, possible adverse effect
Terato rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, possible adverse effect

Chromosome: No data gap, no adverse effect

DNA damage: No data gap, possible adverse effect

Neurotox: Not required at this time

-----**Note, Toxicology**

**one-liners are attached**

\*\* indicates acceptable study

**Bold face** indicates possible adverse effect

File name T881201, revised by J. Gee

## II. TOXICOLOGY SUMMARY

### CHRONIC RAT

013 038421 [reviewed as 925969] Title: Initial Scientific and Mini-economic Review of Folpet. (Arthur D. Little, 6/75) Brief summary of a 1957 study at Hazleton. Rats were fed at 1000, 3200 or 10,000 ppm. No tumor formation identified in summary but no data.

Remsen (Gee), 4/1/85

EPA 1-liner: No CORE grade. Oncogenic NOEL > 10,000 ppm, systemic NOEL = 3200 ppm (increased spleen and testicle weights at 12 mos., increased thyroid weights at 17 mos.)

### CHRONIC DOG

013 925969 Title: Initial Scientific and Mini-economic review of Folpet. (Arthur D. Little, 6/75) Very brief summary of a 1961 study at IBT. Folpet, 90%, fed to beagle dogs, 3/sex/group, at 0, 250, 1000 or 1500 mg/kg for 17 months. No data. Remsen

(Gee), 4/1/85

\*\* 070, 072, 074, 078 047414, 048848, 051369, 055536 "A One-year Subchronic Oral Toxicity Study in Dogs with Folpet Technical." Project No. 82-2677. (Biodynamics, 4/17/86) Folpet technical, SX-1388, 89.5%; given in gelatin capsules at 0, 10, 60 or 120 mg/kg/day; 6/sex/group; nominal NOEL = 10 mg/kg/day - actual 8.95 mg/kg/day (not corrected for purity) (decreased food consumption, decreased weight gain, some blood parameters), acceptable. No chronic effects reported. Initially reviewed by Parker, 11/14/86, as

unacceptable because volume II (document 191-074) was not submitted. Record 055536 contains four analyses over the period of the study. Gee, 3/20/87.

COMBINED RAT

005 925955 (1981, Hazleton Labs). 12 month progress report. See 41758-64.  
Remsen (Gee), 4/1/85

EPA 1-liner: Supplemental for interim report. Rats were fed 0, 200, 800 or 3200 ppm.

**\*\* 052-58 041758-64** "Combined Chronic Oral Toxicity/Oncogenicity Study in Rats, Chevron Folpet Technical [SX-1388]: Final Report." (9/30/85, Hazleton, Project No. 2107-109).  
Folpet, 89.5%, SX-1338; 60/sex/group were fed 0, 200, 800 or 3200 ppm in the diet for 105 weeks; NOEL = 800 ppm (by Chevron) but = 716 ppm accounting for purity; Adverse effects on stomach, especially on glandular portion (hyperkeratosis/acanthosis; erosion/ulceration).  
Initially reviewed as unacceptable but upgradeable with submission of diet analysis by Chevron. Diet analysis is especially important since instability under these conditions is noted in the report, pg. 5. Calculation of the compound consumption uses the nominal amount and does not account for 89.5% active ingredient or for actual diet content. Diet analysis is in Record #50551, Document 191-073, upgrading the study to acceptable. Poor randomization of animals by body weight at the start of the study so that the treated groups of males were -2 to -5% lower than controls. No historical ranges for hematology/urinalysis/clinical chemistry are included in the report. No justification of the high dose with data to support a maximum of 3200 ppm since LD50 is >10,000 mg/kg. [See 925953 for subchronic study by Hazleton -- this report does not really substantiate the 3200 (2684 corrected for purity) used in this study. All tables, however, are missing.] Clinical observations detected no treatment effect. Body weight differences did not increase over time.

Stomach effects:		Control		200		800		3200 ppm		
hyperkeratosis/ acanthosis		M	F	M	F	M	F	M	F	
53 weeks		0/10	0/10	0/10	1/10	1/10	1/10	1/10	2/10	unsched.
6/27	3/19	0/13	4/21	6/18	7/19	12/19	15/20			
105 wk sac		2/23	4/31	3/37	1/29	4/32	3/31	22/31	22/30	

erosion/  
ulceration

53 weeks	0	0	0	0	1	1	3	0
unsched.	4	1	0	1	2	1	3	3
105 wk sac	0	1	0	1	3	2	4	5

Thyroid:

"C" cell hyper plasia	3/23	9/31	6/37	9/29	3/32	8/31	6/31	3/30
"C"cell aden- oma/carcinoma	0	3	8*	5	4	3	4**	1
Follicular cell ad/car	2	1	0	0	0	0	2	2

\* 0.015 by Fisher's exact

\*\* 0.54 " "

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Gee, 6/24/86

There appears to be definite evidence for a chronic effect on the stomach and equivocal evidence for an oncogenic effect in the thyroid. Studies in mice, however, show that folpet

is a carcinogen in the GI track of that species. The difference could be species specific or dose dependent. Both rat and mouse show a response in the same system.

ONCOGENICITY, RODENT

013 925969 Brief summary, initial review of misc. studies.

ONCOGENICITY, MOUSE

013 046835 "Initial Scientific and Mini-economic Review of Folpet." (Arthur D. Little, 6/75) Brief summary of 1969 study by Innes et al. published in J. Nat. Cancer Inst. 42: 1101 (1969). Mice were given 603 ppm for 18 months. Negative for tumors.

002 925956-57 Protocol only for 037929-38. Remsen (Gee), 4/1/85.

011 925958 Identical study to 037929 but with all appendices missing.  
Remsen (Gee), 4/1/85.

**\*\* 023-32 037929-037938** Title: Lifetime Oncogenic Feeding Study of Phaltan Technical (SX-946) in CD-1 (ICR Derived) Mice. (8/24/82, Chevron Env. Health Center). Folpet, 93%. Fifty-two/sex for controls and 80/sex/group were fed 0, 1000, 5000 or 12,000 ppm in the diet for 113 weeks; Swiss CD-1 mice; NOEL <1000 ppm for oncogenic effect if "all tumors" are considered and = 1000 ppm for intestinal tumors. This study was evaluated initially as complete and acceptable. Reconsideration, however, indicates that a true NOEL cannot be established because all doses are too high for systemic and onco effects. FIFRA guidelines, 1982, for oncogenicity tests do not specifically require a NOEL. The study does provide data for dose responses and, therefore, can contribute to risk assessment. Adverse effects include decreased body weight gain in a dose-dependent manner and also for food consumption in the early weeks.

Tumors	Control		1000		5000		12,000	
	(104)		(80)		(80)		(80)	
	M	F	M	F	M	F	M	F
benign	45	31	31	18	35	18	34	23
malignant	9	20	17	19	17	18	44	45
Duodenal neoplasms								
(%)	1	0	3	2	12	10	51	51
Jejunum neoplasms	0	0	2	0	2	0	13	7
(%)								

Aprogression from hyperplasia to malignant tumor was seen at 5000 and 12,000 ppm in the intestinal mucosa.  
Gee, 2/25/86

EPA 1-liner: Supplementary. Oncogenic NOEL < 1000 ppm (LDT), systemic NOEL < 1000 ppm (LDT) - decreased body weight. Positive carcinogen on the basis of a dose-related increase in incidence of intestinal adenomas and adenocarcinomas in both sexes. These neoplasms are rare in CD-1 mice. Results for folpet study controls should be separated from the combined controls of the report and statistical analyses should be made with this single set of controls.

\*\* 062-66 041768-72 "Oncogenicity Study in the Mouse." (9/19/85, Life Science Research Israel Ltd.). Folpet, 88-89%, was fed in the diet at 0, 1000, 5000/3500 or 10,000/7000 ppm for 2 years; B6C3F1 mice; NOEL ≤ 1000 ppm (uncorrected) for onco and for systemic effects (skin). The doses were changed at week 21 because of toxicity. Stomach and duodenal neoplasms, lymphomas are reported as well as skin hyperkeratosis plus other skin (continued on next page) effects. Although a NOEL was not established, one is not essential for onco studies (see under 41758-64). Considering the purity but not the diet analysis (presented in the report), the NOEL is ≤ 800 ppm.

Duodenal lesions	Control		1000		3500		7000	
nodule (/52)	1	3	2	1	16	5	24	6
retraction/restrict.	0	0	1	1	7	6	19	9
distention/enlarg.								
dilatation	0	1	3	1	11	4	17	4
atyp. hyperplas.	0	0	8	1	35	17	37	23
adenoma/carcinom.	0	1	4	2	17	10	25	19
skin								
hyperkeratosis/ acanthosis	-		*		**		***	
esophagus								
hyperkeratosis	-		-		**		***	
stomach								
papilloma	0	2	2	1	3	5	2	7
squam cell carcin.	0	0	0	1	3	0	1	0
hyperkeratosis	-		-		*		**	
malignant lymphoma	13	16	11	16	12	19	9	26*

All numbers to the left are for males, to the right for females.

Body weight gain was depressed up to 24% for females in the high dose and 18% for males; lesser depression was noted at the mid dose. The effect was lessened after lowering of the doses. A risk assessment should be conducted on this study and the Chevron mouse study.

Gee, 6/26/86



REPRODUCTION, RAT

013 038429 [initially reviewed as 925969] Title: Initial Scientific and Mini-economic Review of Folpet. (Arthur D. Little, 6/75) Brief summary of report by Kennedy, 1968 - no reference. Eight males and 16 females were fed 0.1% folpet. No data. Remsen (Gee), 4/1/85

\*\* 039-50 037946-57 Title: Two Generation (Two Litter) Reproduction Study in Rats with Chevron Folpet Technical, Socal 2140, Main Report. (9/19/85, Chevron) Folpet, 89.5%; 30 males and 30 females Crl:COBS/CD(SD)CR rats per group were fed 0, 200, 800 or 3600 ppm (nominal) in the diet for 62 days before mating in a two generation, two litter study on reproduction. Reviewed as unacceptable but upgradeable with presentation of justification of the doses selected and individual clinical observations. Justification was submitted in a letter dated 11/25/86, satisfying the major deficiency noted in the initial review. Randomization of the animals seems poor with the high dose group males and females having lower mean starting weights by 5 and 4% respectively. No clinical obs were reported for the F0 and F1b parents. Food consumption was lower in some high dose groups. Pups in F1a and b showed lower weight gain days 0-21 but were approximately the same at birth, hence the decreased gain could be the result of ingestion of solid food later in the period with toxic dose of test article. No adverse effect on reproduction was reported. Dose selection is discussed in a one-page document dated 11/25/86, resolving the major deficiency and upgrading the study to acceptable status. Remsen (Gee), 3/3/86 and 3/25/87

TERATOGENICITY, RAT

013 038427 [originally reviewed as 925969] Title: Initial Scientific mini-economic Review of Folpet. (Arthur D. Little, 6/75) Brief summary of 1969 report by Kennedy et al.

012 925959-60 Pilot and main study identical to 37942-3. No tables of data included with this report. Remsen (Gee), 4/1/85.

\*\* 036 037942-3 Title: Teratology Study in Rats with Folpet Technical, Final Report. (8/23/83, Argus, Protocol 303-001). Folpet, 89.5%; 25/group were given 0, 10, 60, or 360 mg/kg/day (uncorrected for purity or actual content) by oral gavage, days 6-19; maternal NOEL (clinical obs and body weight) = 60 mg/kg; fetotox. NOEL > 360 mg/kg. EPA considered NOEL's to be: trat > 360, maternal (body weight) = 10 mg/kg and fetotox. (incomplete ossification) = 60 mg/kg. These NOEL values do not take purity into account. No adverse developmental effects due to the a.i. are reported; dose selection was based on a preliminary study. It is not clear how much higher a dose could have been used. Gee, 2/28/86 and F. Martz  
EPA 1-liner: Guideline.

**061 041767** Title: Teratology Study in the rat. (11/10/85, Life Science Research Israel Ltd.). Folpet, 91%; Batch 631729; 22/group; 0, 150, 550 or 2000 mg/kg by oral gavage, days 6-15; maternal NOEL = 150 mg/kg; fetal NOEL stated as < 150 mg/kg (reduced ossification of interparietal bones and incidence of angulated ribs). Unacceptable because a NOEL is not established in this study. Food consumption was decreased in the two higher levels and body weight corrected for gravid uterus was -3% and -8% for these doses.  
(continued on next page)

Dose level (mg/kg/day)	Control	150	550	2000
Gravid uterus (g)	81.9	77.7	65.0 <sup>c</sup>	68.5 <sup>b</sup>
Fetus, small size				
fetal number	20/336	22/316	33/274 <sup>a</sup>	75/277 <sup>c</sup>
litter	9/22	9/22	10/22 <sup>a</sup>	15/20 <sup>c</sup>
Skeletal effects				
anterior fontanelle-				
large				
fetal number	18/171	19/160	35/138 <sup>b</sup>	54/134 <sup>c</sup>
litter	10/22	9/22	14/22 <sup>c</sup>	15/20 <sup>c</sup>
angulated ribs				
fetal number	0	5/60 <sup>b</sup>	4/138 <sup>c</sup>	6/134 <sup>a</sup>
litter		3/22 <sup>b</sup>	3/22 <sup>c</sup>	5/20 <sup>c</sup>
reduced ossification		+	++	+++

<sup>a</sup>  
p < 0.05  
<sup>b</sup>  
p < 0.01  
<sup>c</sup>  
p < 0.001

The results reported here differ from previously reviewed studies in rats where no effect was identified. See 37942-43. A risk assessment should be performed.

Gee, 6/25/86

In the process of preparing the Toxicological Profile for the risk assessment document, these rat studies were re-examined by Drs. T.R. Hathaway, F. Martz and J.Gee. While the differences in results between these studies may be correlated with differences in the spontaneous incidence of skeletal variations, in the absence of historical control data, the possible adverse effect noted in study 41767, will remain.

## TERATOGENICITY, RABBIT

013 038428 [Originally reviewed as 925969] (Arthur D. Little, 6/75) Brief summary of several published studies - Fd. Cosmet. Toxicol. 3: 587-90 (1966) and Toxicol. Appl. Pharmacol. 14: 641 (1969).

017 000771 (2/15/84, Argus). Same study as 37941 with no tables. Remsen (Gee), 4/1/85.

**\*\* 035 037941** Title: Teratology Study in Rabbits with Folpet Technical. (2/15/84, Argus). Folpet technical, 89.5%; given to 20/group by oral gavage at 0, 10, 20 or 60 mg/kg/day; NOEL = 10 mg/kg (maternal and fetal effects). Report is complete and acceptable. Maternal toxicity of decreased weight gain and reduced feed consumption at the intermediate and high doses. Hydrocephaly occurred in the 20 and 60 mg/kg groups but not the low dose group.

Dose level (mg/kg)

	0	10	20	60	Hist. Control
Fetal incidence	0/107	0/73	1/115 (0.88%)	3/65 (4.8%)	3/2160 (0.14%)

Litter incidence	0/6	0/14	1/16 (6.2%)	2/11 (18.2%)	3/285 (1.0%)
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Testing laboratory data (Argus, studies between 4/80 and 8/83)

The effect was noted as a "domed head" in 3/4 affected fetuses. In addition, a skull variation termed irregularly shaped fontanelle was noted in the 4 hydrocephalic fetuses but not any others. Thus, folpet appeared to be teratogenic under the conditions of this study. The incidence of hydrocephaly was significantly greater than control as well as higher than historical control values. Folpet, however, caused maternal toxicity at the two higher doses as shown by one death and the reduced weight gain/food consumption. The contribution of the maternal toxicity to the developmental toxicity needs to be considered. See evaluation for 033 037939 below in which the hydrocephaly was not confirmed but the skeletal variation was confirmed.

Martz, 2/26/86

035 038282      Dose analysis data for 037941.

**\*\* 033 037939      "Teratology Study in Rabbits with Folpet Technical using a "Pulse-dosing" Regimen."** (8/8/85, Argus, Project 303-004). Folpet, 89.5%; 20/group were given 0 or 60 mg/kg by oral gavage, days 7-9, 10-12, 13-15, 16-18 of gestation. NOEL = 10 mg/kg (see 337941). This study was conducted as an extension of the earlier study (#037941) to clarify the teratogenic effects. Only the high dose was used and a modified dosing schedule employed to find if there was a unique "window" of sensitivity. Two hydrocephalic fetuses were recovered -- 1 in days 10-12 and 1 in days 16-18. The former had dilation of the right ventricle only. Neither of these was observable on gross examination whereas 3 of the 4 were in the previous study. Compared with historical controls:

<u>Gestation</u>	<u>Days</u>	<u>Historical Control*</u>
10-12	16-18	

Fetal incidence:	1/113 (0.88%)	1/88 (1.14%)	5/1879 (0.27%)
Litter incidence:	1/15 (6.7%)	1/14 (7.1%)	5/250 (2.0%)

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\* Testing laboratory data (Argus, studies between 1982 and 1984)

No definite "window" was found as fetuses were not in the same or adjacent periods. In addition, the incidence was less than previously found with 2/201 (1.0%) versus 3/64 (4.8%). In addition, the updated historical control was about twice that in the previous study. As a result of these considerations, the present study discounted the association of hydrocephaly with folpet treatment.

In terms of skeletal findings, a slight but significant increase in the incidence of irregularly shaped fontanelle, a skull variation, occurred in days 13-15 group. This variation was also noted in the previous study in the high and mid-dose groups.

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	Present study			Previous study		
	Folpet	Control	Hist. Control <sup>a</sup>	High	Int.	Hist. Control <sup>b</sup>
Fetal incidence	13/107 (12.12%)	5/112 (4.46%)	6/1879 (0.32%)	3/65 (4.62%)	1/115 (0.87%)	2/2162 (0.09%)
Litter incidence	3/15 (20.0%)	2/18 (11.11%)	5/250 (2.0%)	2/11 (18.2%)	1/16 (6.3%)	2/285 (0.7%)

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- a Studies done between 1982 and 1984
- b Studies done between 4/80 and 3/83

A treatment relationship was indicated. Although the hydrocephaly was not substantiated, the skull variation was repeated. Martz, 4/21/86. Document 191-084 contains a rebuttal dated 9/18/87 in which the irregularly shaped fontanelle in the mid and high dose groups are attributed to "normal genetic variation." No change in status. Gee, 12/1/88.

033 37940      Dose analysis data for 37939

059 41765      Pilot study for 41766

\*\*      060 041766      "Teratology Study in the Rabbit." (12/26/85, Life Science Research Israel Ltd.). Folpet, technical, 91.1%; 14 New Zealand white rabbits per group were given 0, 10, 40 or 160 mg/kg by oral gavage, days 7-19; NOEL (maternal) = 10 mg/kg (uncorrected); Fetotox NOEL = 10 mg/kg (uncorrected); No fetotoxicity without maternal toxicity; skeletal effects (reduced ossification of several sites) at high dose, small fetuses increased and gravid uterine weight reduced at mid- and high-doses.

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	Control	10	40	160 mg/kg
Small fetus:				
Fetal incidence	4/123	0	2/114	18/94
Litter incidence	3/14	0	2/14	6/12
Skeletal ossif:				
reduced/irreg.				
sternebrae				
Fetal incid.	1	1/120	8	9
Litter incid.	1	1/14		
appendices				
Fetal incid.	26	19	28	40
Litter incid.	10	7	10	10
vertebral centra				
Fetal incid.	0	1	2	5
Litter incid.	0	1	2	5

This report contains no indication of hydrocephaly and the skeletal effects are seen in the presence of maternal toxicity at the high dose, especially. Maternal toxicity was expressed as severe depression of food consumption and body weight gain and a somewhat increased rate of post-implantation loss at the high dose. The mid dose had decreased body weight gain. Acceptable with no adverse effect. Gee,6/26/86

In preparing the Toxicological Profile for the risk assessment, Drs. T.R. Hathaway, F. Martz and J.Gee re-examined these studies. Based on the weight of evidence provided collectively, a possible adverse effect was not confirmed in the rabbit. The developmental NOEL is the same



as the maternal NOEL (10 mg/kg/day) and, therefore, Folpet does not appear to be a unique hazard to the developing rabbit fetus.

#### TERATOGENICITY, OTHER SPECIES

021 026992 (4/11/85, Health Effects Research Lab., EPA) MOUSE. Folpet, 87.0% technical. Eighteen female CD-1 mice (shipped pregnant) were given 0 or 100 mg/kg by inhalation, days 6-15, 4 hr/day (not by nose only). Unacceptable - single dose, 4/18 deaths. No teratogenic effect reported. Very limited data for evaluation. Remsen (Gee), 9/3/85

013 038430 [initially reviewed as 925969] Brief summary, initial review of misc. studies. Monkey.

**013 038426** [initially reviewed as 925969] Brief summary, summary of a publication by J. F. Robins in Toxic. Appl. Pharmacol. 16: 24-34 (1970)

GENE MUTATION

**013 925969** Brief summary, initial review of misc. studies

**018 016829** Title: S-1261, The Potential of Technical Phaltan (CALHIO) and Technical Phaltan (Port de Bouc) to Mutate TA100, a Histidine-deficient Strain of Salmonella typhimurium. (7/26/78, Chevron). Folpet technical, no purity stated. Strain TA100 was exposed to 0.1, 1.0, 10 or 100 ug/plate in duplicate; no activation system; no individual plate counts. Mutagenic effect with a dose response. Remsen (Gee), 3/29/85

**\*\* 018 016827** [Review sheet erroneously numbered 16828] "Evaluation of selected Pesticides as Chemical Mutagens." (9/15/76, SRI). Folpet, 88 - 90% (see document 191-084, record 062735, for purity) Salmonella strains TA1535, TA1537, TA1538 and TA100; 0, 1, 5, 10, 25, 50, 100, 500 or 1000 ug/plate with and without activation. No individual plate counts. TA98 not included. Tested at least 3 times. Remsen (Gee), 3/29/85.

**\*\* 018 038373** [Review sheet erroneously numbered 16827] "Evaluation of Selected Pesticides as Chemical Mutagens." E.coli. (9/15/76, SRI). Folpet, 88 - 90% (see document 191-084, record 062735 for purity) E. coli WP2 (uvr<sup>-</sup>, 0. 0.5, 1, 5, 10, 25, 50, 100 ug/plate, in triplicate, with and without activation. No individual plate counts, minimum of 3 plates per test; Positive mutagenic effect reported. Remsen (Gee), 3/29/85.

**267-055 027080** "Microbial/Mammalian Microsome Mutagenicity Plate Incorporation Assay: Comparison of Captan Technical, Chevron Folpet Technical and Chevron Captafol Technical." (Chevron, 12/18/84, SOCAL 2042) Salmonella strain TA100, 25 ug/plate without addition or with glutathione or cysteine added in a series of ratios; presence of sulfhydryls decreased reversion rate; no activation; supplementary information.

\*\* 018 016835 "Mutagenesis Screening of Pesticides using Drosophila. (8/77, Warf).  
Folpet, no purity stated. Sex-linked recessive lethal, Canton-S males were given 0, 3 or 3000  
ppm in the diet for 48-72 hours and mated with FM6 females to produce 4 broods; Missing  
information on numbers of males. Remsen (Gee), 4/1/85

MUTAGENICITY, CHROMOSOMES

037 037944 Exact duplicate of 925964.

002 925964 Dominant lethal, rat. (1/8/80,Chevron). Folpet, 97.3%; 20 male rats  
(Osborne-Mendel) were given 0, 50, 100 or 200 mg/kg/day, 5 consecutive doses by oral gavage  
and mated over seven weeks, 1:1. Unacceptable (no rationale for dose selection, no indication  
of toxicity, inadequate number of mated females.) Not upgradeable. Remsen (Gee), 4/1/85  
EPA 1-liner: No CORE grade. Negative mutagen.

\*\* 018 016830 Dominant lethal, mouse. (1976, SRI) Folpet, no purity given. Twenty male ICR/SIM mice were given 1250, 2500 or 5000 mg/kg in the diet for seven weeks, then mated with 2 females/week for 8 weeks. Individual data missing. Dietary intake not measured. Note: This is an early review and, if done with present SOP, would NOT have been evaluated as acceptable. However, in view of the previous dominant lethal in rats, also negative, the two together can be considered as establishing no adverse, dominant lethal effect. Remsen (Gee), 3/29/85.

017 000770 Partial duplicate of 037945 with all data missing. See also 038 37945, rereviewed 2/27/86. Remsen (Gee), 4/1/85

038 037945 "In vivo Cytogenetics Study in Rats, Folpet Technical (SX-1388)."  
(10/28/83, EG&G Research) Folpet technical, 89.5 % (see 191-084, record 062905 for purity of SX-1388); Sprague-Dawley rats, 4/sex/group were given 0, 150, 1500 or 2000 mg/kg by oral gavage in a single dose, then sacrificed at 6, 24 or 48 hours. Diarrhea was noted in the treated groups. In a range finding study, no deaths occurred up to 1.6 g/kg bw. Initially evaluated as not acceptable but upgradeable with the submission of purity of test article and lot number. Also needed is an explanation of how the mtd was determined from the data presented in the range-finding study since it would appear that a much higher dose could have been used. Mitotic index gives no consistent indication of cytotoxicity. No increase in aberrations is reported. Major question was dose selection. Gee, 2/27/86. Document 191-084 contains a discussion of the dose selection but the study remains unacceptable based on inadequate dose - 5 g/kg is the "limit" test if a compound is of low toxicity. No change in status. Gee, 12/1/88.

DNA REPAIR

\*\* 018 016828 "Evaluation of Selected Pesticides as Chemical Mutagens, In vitro and In vivo Studies." (9/15/76, SRI) Folpet, purity not stated. E. coli strains W3110 and p3478 (pol A<sup>-</sup>) and Bacillus subtilis strains H17 and M45 were exposed to 0.1 mg/disk, minimum of three plates. No rationale for concentration selection, metabolic activation not used. Report lacks details. NOTE: This is an early review and would not be considered acceptable using current evaluation standards. In view of the positive findings, however, the deficiencies were overlooked in the initial review. Remsen (Gee), 3/2/85

018 016831 "Evaluation of Selected Pesticides as Chemical Mutagens, In vitro and In vivo Studies." Brief summary of UDS in Human fibroblast, WI-38 (9/15/76, SRI). Folpet, no purity stated. Cells were exposed to 0, 10<sup>-8</sup>, 10<sup>-7</sup>, 10<sup>-6</sup>, 10<sup>-5</sup> and 10<sup>-4</sup> M without activation and to 0, 10<sup>-5</sup>, 10<sup>-4</sup> and 10<sup>-3</sup> M with activation. Report indicated a 2-3 fold increase in dpm/ug DNA purified from replicate cultures with activation. Unacceptable due to number of replicates, missing information. Remsen (Gee), 3/29/85

018 38371 Identical to above record.

#### MISCELLANEOUS GENETIC STUDIES

084 062903 "Updated Summary of Results of Mutagenicity Testing of Folpet Technical (Phaltan)." (Chevron Chemical Company, 1/2/86) Review of in vitro and in vivo studies in the literature and unpublished, with 70 citations. No attempt has been made to compare the studies on file at CDFA with those reviewed. Gee, 12/1/88.

#### NEUROTOXICITY

Not required at this time.